II. REMARKS

Formal Matters

Claims 6-8 and 15-24 are pending.

The Applicants respectfully request reconsideration of the application in view of the remarks made herein.

The Response in General

The Applicants note that this is the fifth Office Action of this application. In the first Office Action the claims were rejected as anticipated by Kourilsky (BBRC, 1970), in the second Office Action the claims were rejected as obvious over Kourilsky (BBRC, 1970) in view of Guo and in the third and fourth Office Actions the claims were rejected as obvious over Kourilsky (Biochimie, 1977) in view of Brenner. In the present Office Action the claims were rejected as obvious over Brenner in view of Oliva.

The Applicants submit that the claims have not been significantly amended since the response to the first Office Action. However, in every case so far, each art-based rejection has been withdrawn in view of the Applicants' arguments only to be replaced by another, similar, rejection that may be addressed by a similar line of reasoning as the prior rejection. While the Office's willingness to withdraw rejections is acknowledged and appreciated, the Office is respectfully reminded that examination procedures such as those employed by the Office in this case are not supported by the Office's examination guidelines and, in fact, should be avoided (see MPEP § 707.07(g)[1]).

In the prior Office Action, the Applicants showed factual evidence relating to the patentability of the claimed invention, including an undisputed showing of unexpected results (solid experimental data demonstrating that urea is unexpectedly superior to other denaturants in oligonucleotide microarray experiments). The evidence was discussed in detail in a formal interview with Exr. Tung on August 11, 2004 and was sufficient for the withdrawal of the prior rejection under 35 U.S.C. § 103. This factual evidence applies to the current rejection under 35 U.S.C. § 103 with equal or greater force than the prior rejection under 35 U.S.C. § 103. However, none of this evidence, not even the showing of unexpected results, is mentioned in this Office Action.

[1] MPEP § 707.07(g): Piecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references.

The Applicants respectfully submit that this evidence is sufficient for the withdrawal of the current rejection under 35 U.S.C. § 103. Such action is respectfully requested.

The Applicants believe that this current rejection under 35 U.S.C. § 103 may be withdrawn solely on the basis of the foregoing. To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 6-8 and 15-23 are rejected as indefinite for reciting the term "oligonucleotide". The Office states that the length of an oligonucleotide is unclear. The Applicants respectfully traverse this rejection.

The Applicants note the Office is only now questioning its meaning a term that has been present in the claims (including allowed claim 19) since the Applicants response to the first Office Action. As noted above, this is the fifth Office Action in this application.

The Applicants respectfully submit that the meaning of the term "oligonucleotide" in the instant claims would be clear to one of skill in the art.

The term "oligonucleotide" is found in over 129,000 abstracts in NCBI's PubMed database, in the specification of 33,000 issued patents, and in the claims of over 4,500 issued patents. The term "oligonucleotide" is defined in several dictionaries, explicitly defined in the instant specification, and is a term that is widely used by molecular biologists. The term "oligonucleotide" is not a term that could be mis-understood by one of skill in the art.

In view of the foregoing, one of skill in the art would instantly know what an oligonucleotide is, and would therefore recognize what is being claimed without ambiguity. Since this is all that is required to comply with the requirements of 35 U.S.C. § 112, second paragraph, the Applicants respectfully submit that this rejection may be withdrawn.

If this rejection is to be maintained, the Applicants respectfully request that the Office provides more detail about why the term "oligonucleotide", as it is used in the rejected claims, is ambiguous. For example, the Office may be able to illustrate its position by means of an example.

The Office is reminded that the breadth of a claim is not to be equated with indefiniteness (see MPEP § 2173.04). In other words, simply because a wide range of oligonucleotides can be employed in the claimed methods, it does not mean that the term "oligonucleotide", as used in the instant claims, is indefinite.

The Applicants respectfully submit that this rejection has been adequately addressed by the foregoing discussion. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C § 103

Claims 6-8, 15-18 and 20-24 are rejected under 35 U.S.C § 103 as assertedly obvious over Brenner (USPN 5,604,097) in view of Oliva (BioTechniques, 2001 31:74-76). Specifically, the Office argues that one of skill in the art would combine Brenner's asserted tagged oligonucleotide array hybridization methods with Oliva's urea-based in situ hybridization methods to provide the claimed invention. The Applicants respectfully traverse the rejection.

The Applicants respectfully submit that the Office has mis-characterized the teachings of Brenner, and, as such, one of skill in the art could not combine Brenner and Oliva in the manner suggested by the Office.

Brenner discloses a method in which a compound is labeled with an oligonucleotide tag, the labeled compound is contacted with a sample, and labeled compounds that are bound to the sample are sorted and identified by means of their oligonucleotide tag. As discussed in col. 17, lines 5-26, the sequence of tag is determined by DNA sequencing.

This rejection is solely based on an assertion that Brenner discloses an array of oligonucleotide tags. However, in contrast to the statements made in this Office Action, at no point does Brenner disclose an array of oligonucleotide tags, or even, for that matter, any oligonucleotide tag that is covalently linked to a solid support. The positions to which the Office refers in support of its statements (col. 12, lines 40-47; col. 13, lines 7-9 and col. 35, lines 1-18 and col. 13, lines 52-58) refer to solid supports linked to tag *complements* and not solid supports linked to the oligonucleotide tags themselves.

Accordingly, the Office Action fails to teach a feature of the claims: an array of oligonucleotides. This rejection may be withdrawn on this basis alone.

Further, Brenner directly teaches away from the claimed invention, and, as such, cannot be properly combined with any other reference to render the claimed invention obvious.

Most of Brenner's background section is spent discussing several problems associated with multiplex hybridization assays. Brenner states in col. 2, lines 2, lines 29-32: "**Such problems have made the simultaneous use of multiple hybridization probes** in the analysis of multiple or complex genetic loci, e.g., via multiplex PCR, reverse dot blotting, or the like, **very difficult.**" (Emphasis added).

As a point of fact, in col. 2, lines 22-28 Brenner warns that the use of reagents that alter base-specific stability of nucleic acid duplexes (of which urea would be an example) in a hybridization assay would be undesirable because their **effects are limited** and then can be **incompatible** with further manipulations.

In fact, in col. 2, lines 44-50, Brenner presents his invention as a system which "minimized the occurrence of false positives and false negative signals **without the need to employ special reagents for altering natural base pairing**". (Emphasis added).

On the basis of Brenner's extensive warnings about adding agents that alter base pairing to hybridization buffer, one of skill in the art would not combine urea, a destabilizing agent, into Brenner's methods.

In other words, Brenner explicitly warns against the use of reagents that alter base-specific stability of nucleic acid duplexes. Since urea is employed in the rejected claims and is one example of one of Brenner's forbidden reagents, Brenner's disclosure teaches away from the claimed invention.

Accordingly, Brenner explicitly teaches away from the claimed invention and cannot, under any circumstances, be used in combination with any other reference (including Oliva) to render the instant claims obvious.

This rejection may also be withdrawn on this basis.

Further, the Office is reminded that the MPEP and current caselaw is explicitly clear about rejections based on obviousness: **the prior art must suggest the claimed invention.** This is explicitly set forth in MPEP § 2145.X.C and explained in great detail in MPEP § 2143.01. It is a central tenet of patent law.

In this case, the Office has combined unrelated references and has argued that the claimed invention would be obvious. According to the Office, the first reference (Brenner), discloses **DNA/DNA** hybridization methods using an **oligonucleotide array**. The secondary reference (Oliva) discloses **RNA/RNA** hybridization methods using **paraffin embedded**

tissue samples. The Office has merely asserted that the claimed invention would be obvious in view of the combined references because it would obviously yield a desired result (reduced hybridization temperature). However, among other things, **none of the cited references suggest what is being claimed**. Accordingly, the cited prior art therefore *does not* suggest the subject matter of the rejected claims, and pursuant to current caselaw and the MPEP, this rejection may be withdrawn.

Simply put, the prior art fails to suggest a central feature of the rejected claims: the use of urea in an oligonucleotide array hybridization assay.

The Office appears to be taking a position that it would be obvious to hybridize a sample to an oligonucleotide array in a urea buffer in because it would reduce the hybridization temperature of the reaction.

However, merely stating that the instant invention is suggested because it would decrease the temperature of a hybridization does not render the instant invention obvious. Stated another way, an elegant and straightforward method such as that being claimed does not simply become obvious because there is a need for such a method.

As a point of fact, none of the cited references even recognizes a problem that could be solved by the claimed invention. The need for the claimed invention is simply not set forth in the prior art references, especially in view of Brenner's direct teaching away from the use of agents that modify the hybridization of polynucleotides.

Finally, the Applicants submit that the claimed method provide unexpected results.

The claimed urea-based methods provide enhanced results which could not have been predicted from the teachings of the cited art, in comparison to equivalent methods using other denaturants. As evidence of these advantages, Applicants have previously submitted a post-filing publication demonstrating the unexpected benefits of the presently claimed methods and compositions. The date appearing on this publication is "October 2002", well after the filing date of the instant application.

This publication, which is a product literature brochure from MWG Biotech AG (previously submitted as Exhibit C), describes hybridizing a microarray of oligonucleotide probes with target nucleic acids from rat liver and kidney, in a variety of different denaturants, including salt (e.g., SSC and SSPE), two different concentrations of formamide, and urea. The results from this experiment are shown on page 2 of the publication in the

graph entitled Fig. 1. Quoting from the publication: "The slide-to-slide correlation of ratios were clearly better in urea-buffer (see Figure 2)."

These data demonstrate that urea buffers are superior to buffers containing other denaturants (even those buffers containing salt) in oligonucleotide microarray experiments. This superiority could not have been predicted by the teachings of Brenner or Oliva. Accordingly, one of skill in the art could not have predicted the success of the presently claimed invention.

This showing of unexpected results, alone, should be sufficient, according to the MPEP §716.02 and current law, for withdrawal of this rejection.

With the foregoing discussion in mind and pursuant to MPEP § 707.07(f) the Applicants submit that that the Applicants prior statements, including the showing of unexpected results, should be accepted at face value if not rebutted.

The Applicants respectfully submit that this rejection has been adequately addressed. In view of the foregoing discussion, the Applicants respectfully request withdrawal of this rejection.

A Notice of Allowance is respectfully requested without any further delay.

Agilent Ref: 10010819-1
United States Application Serial No. 10/001,688

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone Timothy Joyce at (650) 485 4310.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 that may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,
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